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Genetic and Environmental Effects on Fat Distribution: The Healthy Twin Study

지방 분포와 관련된 유전 및 환경적 요인 분석

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Abstract

Genetic and Environmental Effects on Fat Distribution: The Healthy Twin Study

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People commonly think that individuals have different fat distribution and this characteristic was inherited. Also, there are a variety of methods on managing regional fat. However, most fat distribution studies are actually not about regional fat but about abdominal fat. In the case of abdominal obesity, this is the leading cause of obesity-related diseases. As a result, abdominal fat researches have mainly studied and studies of fat distribution on other areas are very poor.

The twin cohort study in Korea consists of 3461 individuals including 689 families, 550 pairs

of identical twins, and 124 pairs of dizygotic twins. Among 3461 people, 3435 people measured by dual-energy X-ray absorptiometry (DXA) were included in this study. And, fat regions of participants used in this study are arms, legs, head, and trunk.

To investigate the correlation with fat mass and obesity indices, we used spearman correlation analysis. The association with regional fat distribution and several environmental factor was analyzed using multiple regression with mixed model. And, genetic factor which has effects on regional fat distribution was analyzed by two method; intraclass correlation coefficients(ICC) and heritability analysis using variance component model.

According to results of this study, correlation between fat distribution and waist hip ratio, which is an important indicator of abdominal obesity, was little and portion that environment has effects on regional fat distribution was small. However, although several environmental factors were not associated with regional fat, genetic factor has strong association with regional fat. This could be confirmed by ICC analysis and heritability analysis. Especially, because total fat was correlated with 4 regional fat, this explained a large portion of regional fat in heritability analysis. But, after the effects of total fat were excluded, additive genetic effects still accounted for the remaining effects on fat distribution. This means that genetic factor among several factors have significant effects on regional fat distribution and common idea that there is genetic predisposition on gaining fat by region could be proved to be the truth to some extent.

Until now, although the research on central obesity have been done mainly, results on

regional fat distribution in this study could help us to understand more overall fat distribution among Koreans. According to these results, there is strong genetic effects on regional fat distribution. This could make us more investigate further study such as association between fat distribution and hormones or genome-wide association study on regional fat distribution. Therefore, these follow-up studies will be able to provide some directions on managing regional fat.

Keywords: Regional fat, DXA, environmental factor, heritability, Family-Twin study

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Introduction

Obesity is a problem of the public health worldwide. Specially, obesity problem is becoming more common among people and adds heavy load on to our societies. Many studies have reported reasons of obesity that include not only genetic factor(1) but environmental factor such as physical activity, smoking, alcohol consumption (2), socioeconomic status (3) and etc. these studies used obesity indices to investigate reasons of obesity. Studies on the obesity have performed in various aspects. Genetic predisposition to obesity has been also found as one topic of these studies. In a twin study, the heritability of obesity is 0.45-0.81 in male group and 0.72-0.85 in female group(4). Also, it is well known that people with variations in the FTO (Fat mass and obesity-associated protein) gene associated with obesity of children and adult were more likely to be obese. These studies discovered genetic predisposition of obesity using obesity index such as BMI (5-6).

People wanted to know not only about obesity but also gaining regional fat by body composition for their appearance, while genetic factors associated with obesity were well studied like FTO genes. Generally, people think that gaining regional fat by body composition might be influenced by inheritance. Looking at the studies of regional fat distribution to identify whether regional fat distribution has genetic predisposition, these studies investigated various environmental factors like other obesity studies (7). However, fat distribution of these researches was defined not as fat distribution by body composition but as fat distribution of only abdominal region. Although it is important that abdominal obesity can lead to serious ailments(8-10), too many studies of fat distribution almost deal with only abdominal region such as waist circumstance, waist hip ratio android and gynoid type (11-19). Therefore, the studies about understanding overall fat distribution were not found easily. Meanwhile, there are several researches about genetic effects on fat distribution showing results of heritability and genome- wide association. They also used the concept on fat distribution defined as waist circumstances or waist hip ratio (20-22).

Sometimes, the studies of regional fat distribution divided by body composition could be found although they are few. They focused on one regional fat such as arm, leg or trunk, respectively. Despite few researches, some studies among them investigated environmental effects or genetic effects on regional fat distribution. These studies showed that there is genetic effects on regional fat distribution; heritability of arm fat was 0.31(23) and the value of trunk fat was 0.65 (24). In another study, heritability of trunk fat was 0.85 and that of lower body (leg) was 0.81 in elderly group (20). However, these studies about regional fat distribution also have limitation because they focus on one region such as arm, leg or trunk fat distribution.

Therefore, our study helps people to understand overall fat distribution. Also, this study reports how genetic factor influences fat distribution of Korean.

Aim

The aim of this study is to investigate which factor between genetic and environmental factor plays a more important part in fat distribution of Korean. Also, this could discover whether there is genetic predisposition to regional fat by body composition among family. If influence of environmental factor is high, we can know what factor among several environmental factors is mainly associated with fat distribution. From this study, people could understand more about regional fat and take solution for managing fat distribution.

Method

1. Participants

Participants are part of the Healthy Twin Study; the prospective cohort study that has recruited Korean adult twins and their family members based on a nation-wide registry at public health agencies since 2005. They consist of 3461 individuals, which were recruited from Samsung and Busan Baik Medical Center. Among 3461 participants, 3435 individuals who were measured using Dual-energy X-ray absorptiometry (DXA) were included in analysis. Total 3461 individuals consist of 1403 male and 2034 female. This population includes 689 family including spouse, offspring or relatives; monozygotic twin (MZ), 550 pair, dizygotic twin (DZ), 124 pair including one triplet.

To study fat distribution, we selected people who have data of regional fat; Arms fat, 3438 individuals, legs fat, 3437 individuals, head fat, 2661 individuals, trunk fat, 3437 individuals. All participants provided written informed consent.

2. Measurements

Participants responded a questionnaire including demographics, smoking, alcohol consumption, physical activity, income, education and etc.

Smoking group was divided into 3 groups, “Never” (participant has not smoked), “Past” (participant smoked) or “Present” (participant is smoking).

Alcohol drinking habits were divided by intake gram of alcohol per day according to WHO guidance (25-26). Alcohol drinking habit groups consist of 3 groups; “Heavy drinking”, “Moderate drinking”, “Never drinking”. Also, total calorie intake groups were split into 3 groups by 1400 kcal/day and 1800 kcal/day excluding values of < 500 kcal/day.

We used Metabolic Equivalent of Task for estimating physical activity. This score is a measurement of physical activity expressing the energy cost of physical activities and is defined as the ratio of metabolic rate; 1 MET is equal to 3.5 ml $\cdot kg^{-1} \cdot min^{-1}$. 4 METs are equivalent to moderate-intensity physical activity and 6 METs are equivalent to vigorous-intensity physical activity (27). Referencing articles, this study define high activity group and low activity group as >3000 METs and < 600 METs, respectively (28).

In case of income, 2 groups were divided on the basis of a salary of 1.5 million won a month. Education groups were split into 2 groups based on graduation of high school, “above graduation of high school” or “below graduation of high school”.

Waist circumference (WC, cm), hip circumference (HC, cm) and other physical values were measured by standardized instruments. Body composition data including arms fat, legs fat, head fat, trunk fat, and total fat (g) was measured by DXA (Dual-energy X-ray absorptiometry).

3. Statistical Analysis

The summary of common description was presented as mean ± SD of regional fat by categorical variables. Because arms, legs, head, trunk and total fat (g) were not normally distributed according to Kolmogorov–Smirnov test, the fat data was transformed to natural log value. The transformed data was used on analysis of this study.

Using Spearman correlation, relationship between transformed regional fat mass and obesity indices was identified.

To determine the relationship between fat distribution and various environmental factors, multiple regression was performed using mixed model. Family relationship was adjusted as random effect and other environmental factors were used as fixed effect.

Among family relationships, resemblance of fat distribution was quantified by intraclass correlation coefficients (ICC) which was calculated after adjusting for several factors.

MZ twins (monozygotic twins) have same genetic information and DZ twins (dizygotic twins) or siblings share a half of genetic information. Spouse have different genetic information. Using the resemblance of genetic information, genetic factor contributes to 4 regional fat distribution through ICC analysis. The group having higher value of ICC compared to other groups have similar trend of regional fat distribution within group. If MZ group has higher value compared to DZ/Sibling group and Spouse group, this suggests that regional fat distribution is associated with genetic factor.

The heritability analysis could also quantify the association of genetic factor. This value was estimated by Sequential Oligogenic Linkage Analysis Routines (SOLAR) software package (version 6.6.2; http://solar.sfbrgenetics.org/) using variance-component method.

After we measured estimation of heritability quantifying additive genetic effects, unmeasured shared environments, and unique environments, the best-fitting model was determined based on the maximum likelihood estimation. Heritability is proportion of phenotypic variance and was estimated by several models. Among those models, this study used 2 model, AE and ACE model. AE model could explain additive genetic effects (A) and environment effects (E). Another is ACE model that could explain shared effects (C) in addition to additive genetic effects (A) and random individual effects (E). Difference between AE model and ACE model is existence of shared effects(C).

This study used log-transformed 4 regional fat distribution on heritability analysis and conducted heritability analysis with adjusted by age, sex and total fat (g).

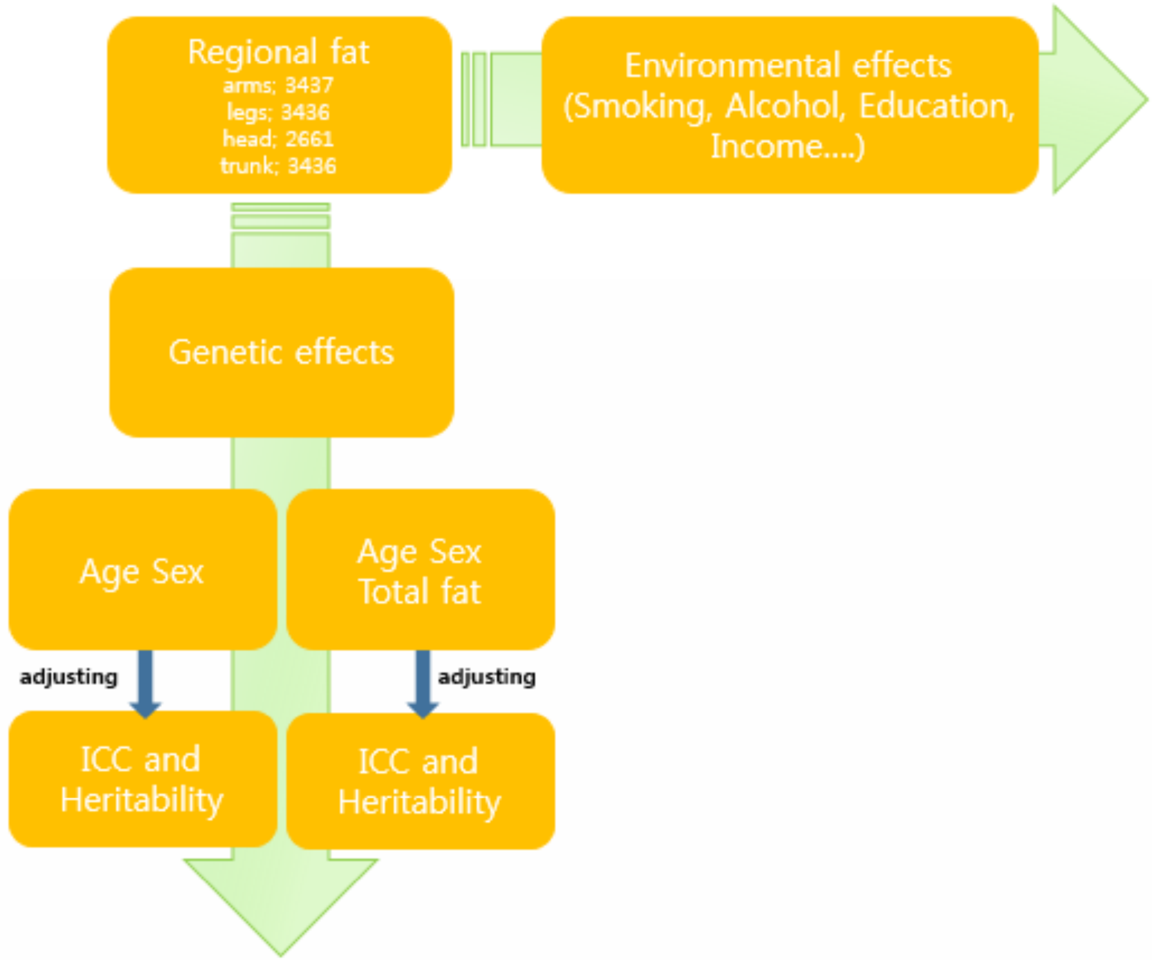
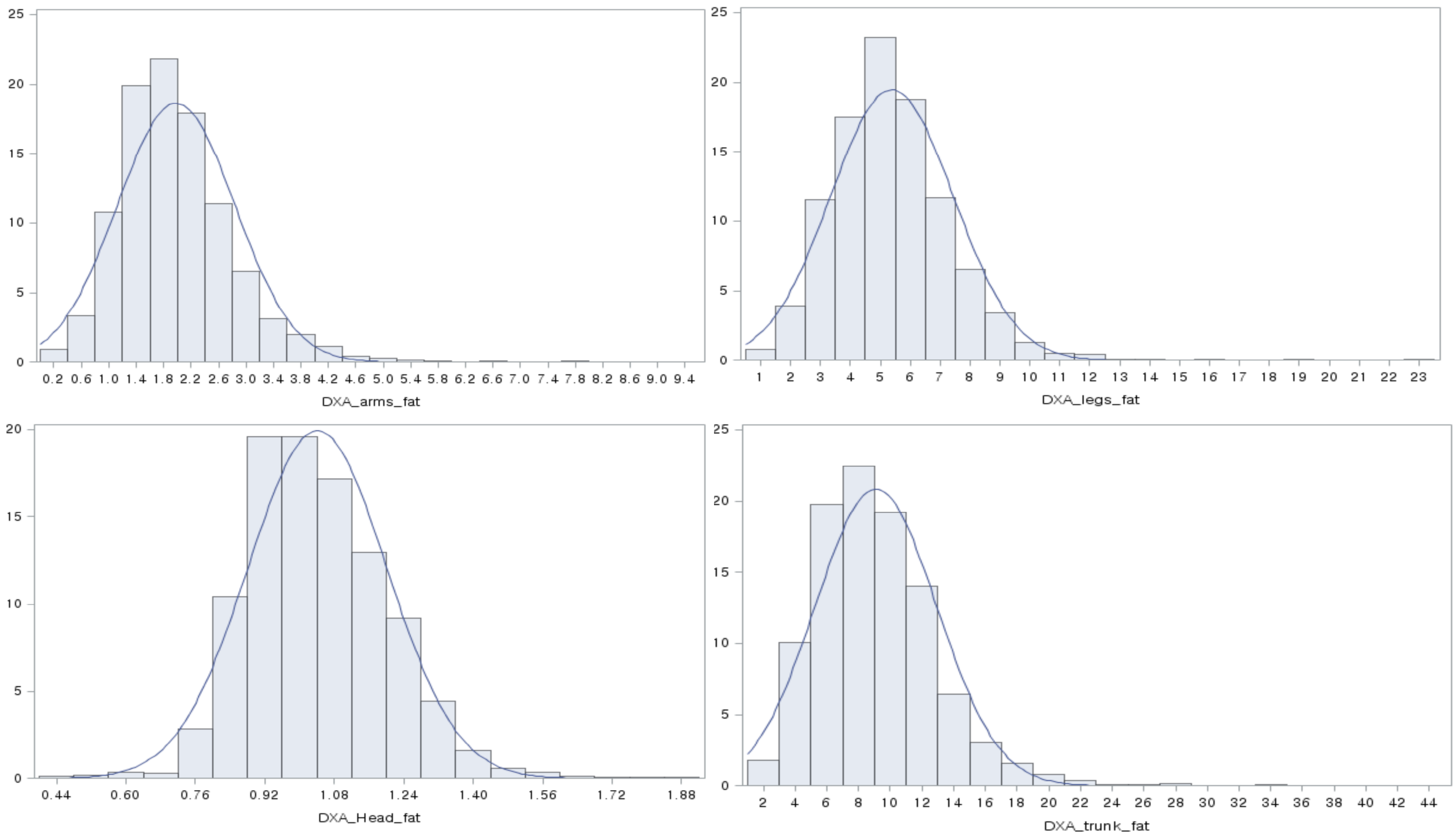


Figure 1. Flow chart of study

Figure 2. Distribution of regional fat (Arms fat, legs fat, head fat, trunk fat)



Results

1. Basic description

At first, table 1 shows means of 4 regional fat that was calculated by sex and several environmental factors; age, smoke alcohol, doing regular exercise, income and education. Results show that mean differences between male and female was definite on any groups.

Also, significant differences between the mean values of each group were shown. Especially, in case of head fat, male have more head fat than female although female have more fat on 3 different regions. However, mean values among male groups for each category didn't show clearer differences than differences of mean between men and women.

The results divided by age groups show that arms, head and trunk fat didn't have any trends according to the age. But, legs fat had trend that fat is reduced gradually with age regardless of sex.

In case of smoking cigarettes groups, people who smoke now did not have more regional fat compared with people who don't smoke. And, groups divided by smoking did not show any trends.

Alcohol drinking habit divided participants into 3 groups; these groups have different trends by sex. In male groups, people who drink alcohol have more fat than people who do not drink alcohol except head fat. But, female groups by alcohol drinking habit have different trend on regional fat. Female group having drinking habit has higher mean values on arm and trunk fat than people who do not have drinking habit.

In total calorie groups, any special trend was not shown on mean value levels.

The groups by physical activity scores did not have any tendency. Also, head fat groups divided by physical activity have no difference between groups. In case of trunk fat, however, difference between low activity group and high activity group of trunk fat have clearer than that of other fat.

In groups by income or education level, there are some trends on 4 regional fat distribution. First, Men earning less than 1.5 million won have more fat on all regional fat, but women groups have different tendency depending on fat region; arms, head, and trunk fat groups show that female participants earning less 1.5 million won have more fat.

Education groups have similar tendency with that of income. Low education level group of male participants has more fat on 4 body composition. But, female group of high education level has more fat than female group of low education group except leg region.

Table 1 Basic description by sex and regional fat

	Arms fat (g)		Legs fat (g)		Head fat (g)		Trunk fat (g)	
	Male	Female	Male	Female	Male	Female	Male	Female
Sex*	1630±779 (1403)	2221±823 (2035)	4364±1994 (1403)	6088±1775 (2035)	1148±148 (1128)	962±118 (1534)	8707±3931 (1403)	9359±3740 (2036)
Age group*								
~29	1668±746 (173)	1946±723 (215)	5100±2060 (173)	6415±1788 (215)	1154±130 (152)	937±115 (188)	8106±4075 (173)	7578±3295 (215)
30~39	1700±888 (482)	2015±749 (729)	4732±2145 (482)	6120±1687 (729)	1168±162 (369)	957±119 (517)	9063±4247 (482)	8293±3407 (729)
40~49	1565±897 (261)	2264±826 (457)	4105±2272 (261)	6110±1832 (457)	1150±159 (207)	960±117 (338)	8538±4238 (261)	9585±3688 (457)
50~59	1626±595 (228)	2545±863 (327)	4011±1474 (228)	6077±1889 (327)	1150±120 (194)	975±117 (266)	8823±3258 (228)	10888±3667 (328)
60~	1542±565 (259)	2495±808 (307)	3762±1394 (259)	5763±1717 (307)	1103±134 (206)	982±115 (225)	8513±3361 (259)	11166±3519 (307)
Smoke*								
Never	1659±721 (397)	2237±818 (1841)	4462±1812 (397)	6120 ±1765 (1841)	1150±150 (333)	963±118 (1383)	8467±3667 (397)	9411±3733 (1842)
Past	1644±769 (503)	2022±668 (79)	4345±2084 (503)	5875±1694 (79)	1128±141 (425)	942±92 (69)	9030±4093 (503)	8524±3255 (79)
Present	1584±834 (496)	2111±982 (114)	4286±2044 (496)	5713±1950 (114)	1167±151 (363)	973±135 (81)	8524±3039 (496)	9114±4104 (114)
Alcohol drinking habit *								
Never	1592±831 (268)	2317±859 (877)	4216±2168 (268)	6042±1790 (877)	1139±137 (214)	971±118 (647)	8426±4255 (268)	9903±3902 (877)
Moderate drinking	1619±733 (926)	2150±793 (1068)	4395±1863 (925)	6147±1786 (1068)	1142±147 (925)	955±117 (826)	8649±3708 (925)	8931±3589 (1068)
Heavy drinking	1726±899 (209)	2145±716 (89)	4440±2288 (209)	5967±1474 (89)	1183±159 (169)	966±118 (60)	9365±4347 (209)	9163±3208 (89)
Total calorie intake (kcal/day) *								

< 1800	1618±700 (710)	2239±799 (786)	4362±1731 (710)	6144±1619 (786)	1156±153 (569)	965±123 (584)	8658±3625 (710)	9325±3651 (786)
1400-1800	1679±871 (309)	2247±927 (480)	4346±2291 (308)	6123±1922 (480)	1139±136 (256)	959±120 (370)	8807±4130 (308)	9332±4109 (480)
500-1400	1494±807 (238)	2167±776 (591)	4051±206 (238)	5942±1812 (591)	1102±157 (175)	951±109 (429)	8336±4192 (238)	9293±3616 (591)
Physical activity *								
High	1560±759 (561)	2226±810 (769)	4096±1924 (560)	5981±1696 (769)	1138±150 (432)	954±117 (586)	8358±3904 (561)	9373±3624 (769)
Moderate	1671±744 (371)	2158±796 (678)	4534±1869 (371)	6008±1681 (678)	1141±159 (306)	953±116 (485)	8821±3595 (371)	8964±3660 (678)
Low	1598±665 (138)	2228±932 (217)	4339±1591 (138)	6257±1901 (217)	1135±154 (110)	964±133 (170)	8905±3509 (110)	9516±4012 (217)
Income *								
<= 1.5 million won	1605±832 (940)	2232±831 (1406)	4234±2084 (940)	6073±1794 (1406)	1148±147 (711)	967±118 (1000)	8577±4101 (940)	9446±3864 (1406)
> 1.5 million won	1729±678 (339)	2179±810 (433)	4710±1821 (339)	6204±1784 (433)	1153±149 (312)	949±112 (386)	9301±3525 (339)	9073±3441 (434)
Education*								
<=high school	1542±772 (716)	2320±856 (1216)	4098±1977 (716)	5981±1822 (1216)	1127±141 (548)	967±122 (878)	8378±3956 (716)	9994±3817 (1217)
> high school	1722±779 (681)	2068±738 (813)	4646±1981 (681)	6246±1693.70 (813)	1168±151 (574)	955±112 (653)	9062±3885 (681)	8394±3394 (813)

Mean+ SD (N)

* P value <.0001 among groups

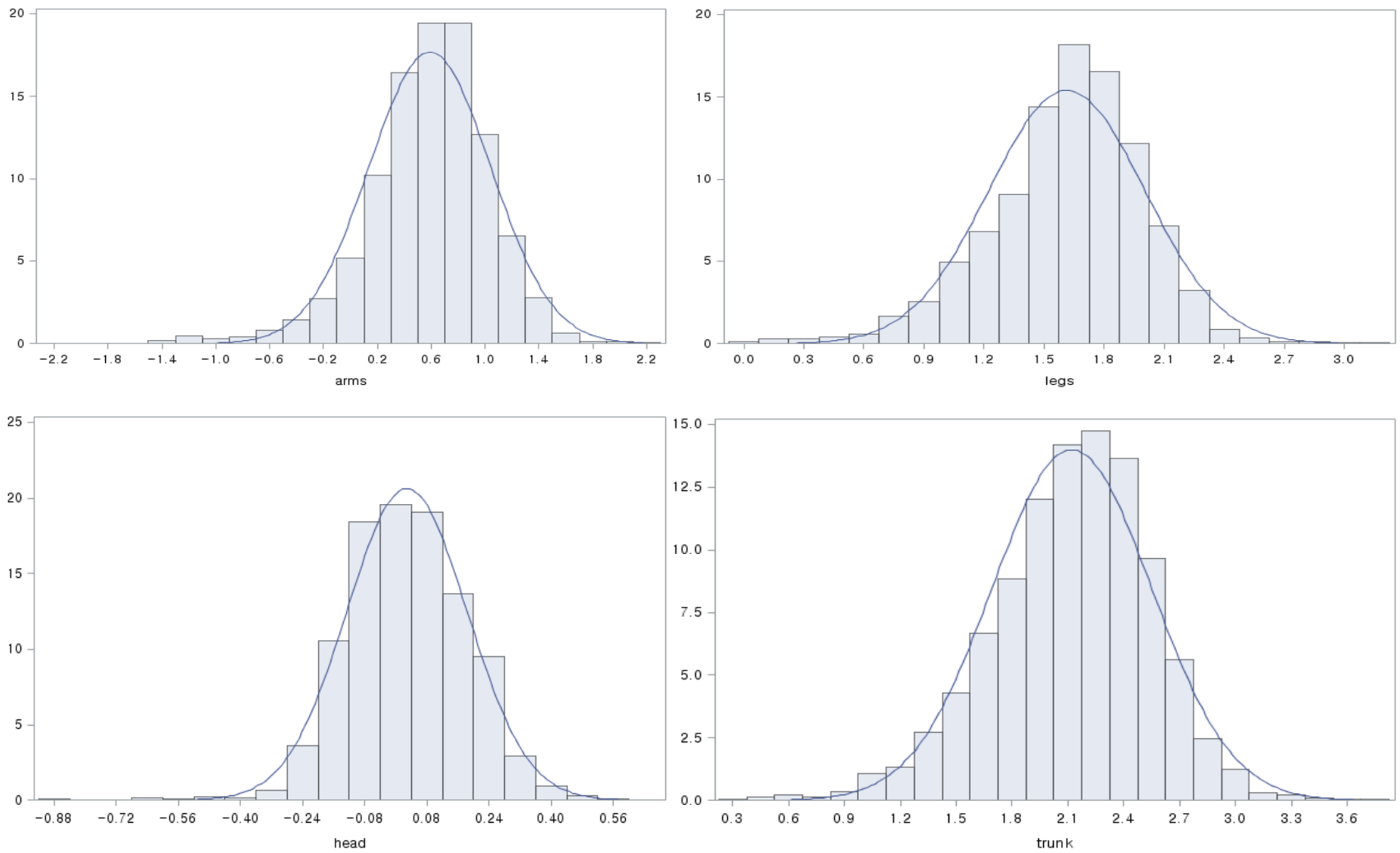


Figure 3. Log transformed regional fat (Arms, legs, head, trunk)

2. Correlation between regional fat and several obesity indices

There are several obesity indices that show degree of obesity; BMI (Body Mass Index, kg/m^2), WC (Waist circumstance, cm), and WHR (Waist hip ratio). The results of correlation revealed whether there is any relationship between these obesity indices and regional fat. Table 2 describes that total fat (kg) had high correlation with 4 regional fat. However, WHR (Waist-Hip-Ratio), one of the important abdominal obesity indicators, had low correlation with 4 regional fat (Spearman correlation coefficient: arms and WHR; 0.27, head and WHR; 0.42, trunk and WHR; 0.50). Although that was not significant, the value of correlation coefficient between leg fat and WHR was negative correlation.

Also, head fat was less associated with total fat than other regional fat (spearman correlation coefficient: male and female; 0.24, male; 0.53, female; 0.54).

Table 2 displays interesting fact that head fat has low correlation with obesity indices overall.

This fact also is shown on Figure 2, which is a correlation plot. In this plot, upper right side and down left side represent shade and pie chart showing the degree of correlation. This plot could also identify relationship between regional fats. Head fat have some relationship with trunk fat. But, legs and arms fat have weak correlation with head fat.

Table 2 Correlation between regional fat and obesity indices

	Arms fat			Legs fat			Head fat			Trunk fat		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total fat	0.84*	0.84*	0.84*	0.81*	0.88*	0.78*	0.24*	0.53*	0.54*	0.93*	0.95*	0.95*
BMI	0.56*	0.70*	0.76*	0.35*	0.63*	0.54*	0.55*	0.52*	0.51*	0.74*	0.76*	0.81*
WC	0.41*	0.68*	0.71*	0.17*	0.59*	0.43*	0.61*	0.48*	0.48*	0.65*	0.77*	0.76*
WHR	0.27*	0.46*	0.52*	-0.03	0.28*	0.16*	0.42*	0.23*	0.29*	0.50*	0.56*	0.59*

* P value <.0001

WC: Waist circumstance, WHR : Waist to hip ratio

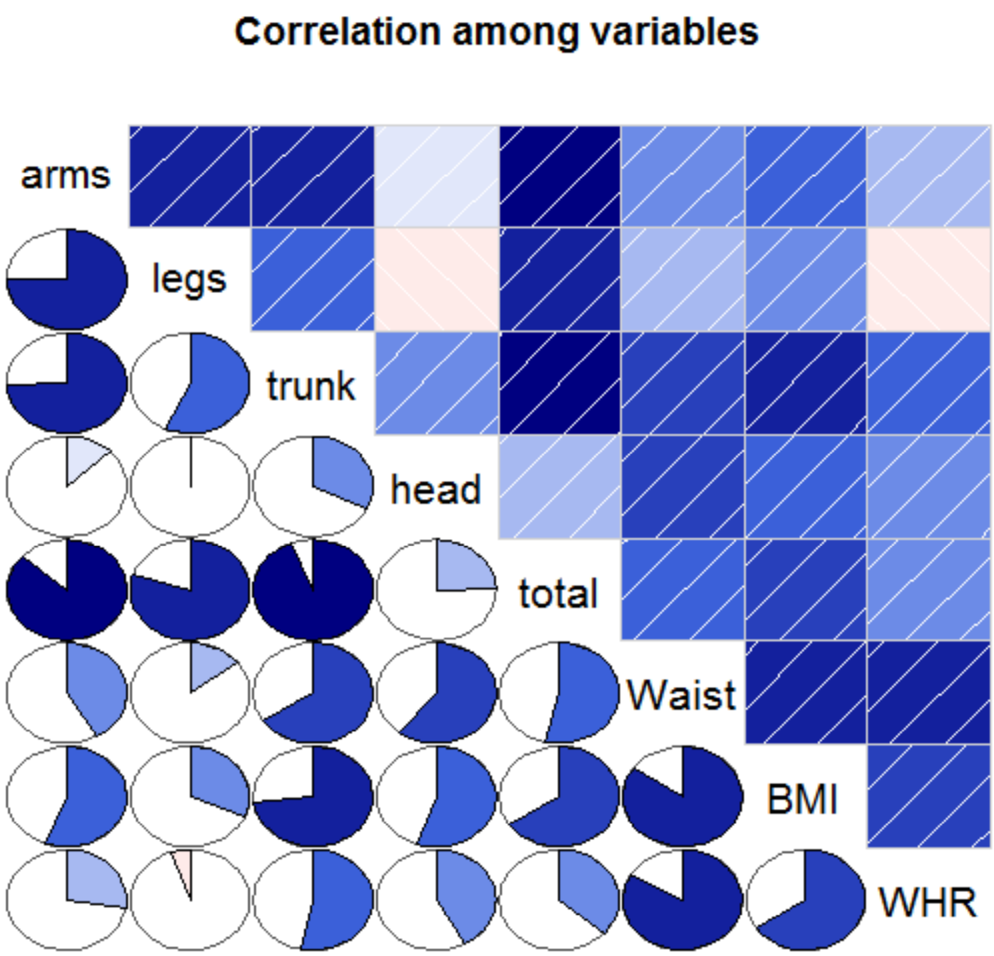


Figure 4. Correlation plot between 4 regional fat and obesity indices

3. Environmental factors associated with fat distribution

Table 3 is a result about environmental factors having effects on fat distribution made by the regression analysis of mixed model. This table shows fat distribution might not be explained by several environmental factor.

While arms and trunk fat increase with age, legs fat decreases with age among people. People who smoke have more head fat regardless of sex. However, same group has less leg fat. Although there was no notable association between alcohol drinking habit and regional fat, trunk fat has significant association with heavy drinking habit on male and female groups.

In case of total calorie intake, this factor was weak associated with regional fat distribution. Table 3 also shows not significant but positive association that increasing total calorie intake gets more fat on 3 region; arms, legs and head fat.

The higher physical activity estimated by MET (Metabolic Equivalent of Task) scores was, the less trunk fat was on both sex. The values of male group were significant.

High income showed significant association with head fat. People who earn more money have more head fat on male and female group. And, arms fat has significant association with income only in male group.

In regards to the education level, low education group among male participants has less head fat than high education group and female group having low education level has more trunk fat than high education group. Especially, this table also shows higher education level in female group has effects on leg fat; low education group in female group has less leg fat. This association is significant. This might be because they who have high education sat in front of desk for a long time. To investigate this speculation, correlation between time sitting on weekdays and legs fat was examined. As a results, supplementary table 1 shows that sitting time has significant positive correlation. But, this correlation was not much higher than correlation between education levels and leg fat.

Looking at the entire table 3, we could find that environmental factors did not have same effect on different regional fat, respectively.

Table 3. Several environmental factors estimated by multiple regression using mixed model.

	Arms fat(Kg)		Legs fat(Kg)		Head fat(Kg)		Trunk fat(Kg)	
	Male	Female	Male	Female	Male	Female	Male	Female
Age(year)	0.000944	0.002197‡	-0.00463‡	-0.0064‡	-0.0004	0.000057	0.003185‡	0.003576‡
Smoke								
Present	-0.02768	0.003034	-0.01195	-0.03546*	0.02653*	0.02852*	0.01357	0.01917
Past	-0.03544	0.000701	-0.03528*	0.008444	-0.01951	0.001595	0.02582*	-0.0021
Never (ref)								
Alcohol drinking habit §								
Heavy drinking	0.007796	-0.00901	-0.04851*	-0.03254	0.009871	0.003073	0.05912‡	0.02923*
Moderate drinking	0.01223	-0.00459	0.000327	0.003557	-0.01975	-0.00401	0.03752†	-0.00414
Never(ref)								
Total calorie intake (kcal/day)								
< 1800	0.02438	0.01734	0.01281	0.008773	0.02399*	0.01531*	-0.01161	-0.01009
1400-1800	0.05036*	0.02144	0.005299	0.01375	0.01729	0.01151	-0.00288	-0.01057
500-1400 (ref)								
Physical activity ¶								
High	0.02334	0.01155	-0.01435	0.000716	0.0211	-0.00533	-0.04429†	-0.00225
Moderate	0.01587	0.01486	0.01632	-0.00779	0.005327	0.000169	-0.04644†	-0.00385
Low (ref)								
Income								
<= 1.5 million won	0.05083†	-0.00626	0.01645	0.01434	0.03272†	0.03746‡	-0.02142	-0.02005†
> 1.5 million won (ref)								
Education								

<=high school	-0.01523	0.002678	-0.00528	-0.03494‡	-0.02804†	-0.00787	0.001856	0.0273‡
> high school (ref)								

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$

Adjusted for age, smoking, alcohol drinking habit, total calorie intake (kcal/day), physical activity(MET; Metabolic Equivalent of Task), income, education and total fat (kg)

§ Heavy drinking groups defined as > 40g/day for male and > 20 g/day for female; Moderate drinking group defined as =< 40g/day for male and =<20 g/day for female

¶ Low activity group defined as 600> MET-minutes/week; Moderate activity group defined as 600<= MET-minutes/week <3000 ; High activity group defined as 3000=<MET-minutes/week

4. Intraclass correlation of regional fat distribution.

Table 4 shows the result of intraclass correlation. Age and sex were adjusted on model 1 and age, sex and other environmental features were adjusted on model 2. Age, sex, and log transformed total fat were adjusted on model 3 and age, sex, total fat and other environmental features were adjusted on model 4. There were differences between model 1, 2, 3 and 4; because there was high correlation between 4 regional fat and total fat, the values of model 2 and 4 (after adjusting total fat) were lower than that of model 1 and 3. However, the values of almost models had similar trends that the intraclass correlation coefficients decreased from MZ twin group to spouse group. These results suggest the lower having shared genetic factor, the lower value of intraclass correlation coefficient. Almost MZ twin group has the highest value (0.4735-0.7741) among different regional fat, while dizygotic twin and sibling group have lower value than MZ twin except the values of arms fat and trunk fat on model 4. And, the intraclass correlation coefficients of spouse group who did not have same genetic factor were the lowest values among several results.

These results describe regional fat distribution of monozygotic twins who have same genetic factor was more relevant than of dizygotic twins and sibling or spouse. Also, 4 regional fat has similar tendency in model 1, 2, 3 and 4, respectively. Among 4 regional fat, the ICC values of arms, trunk and legs have lower than head fat excluding model 4.

Table 4 Intraclass correlation coefficients of regional fat

		ICC				
Model	Trait	MZ	DZ	Sibling	DZ+Sib	spouse
Model 1	Arms fat	0.677754	0.404721	0.205453	0.249528	0.050523
	Legs fat	0.686296	0.332258	0.212869	0.234172	0.050384
	Head fat	0.728951	0.377827	0.338386	0.3501	0.057204
	Trunk fat	0.698032	0.350399	0.209002	0.241062	0.069926
Model 2	Arms fat	0.729659	0.487294	0.200722	0.259498	0.106665
	Legs fat	0.713436	0.455922	0.249974	0.27048	0.120461
	Head fat	0.73309	0.341209	0.330685	0.340046	0.092964
	Trunk fat	0.727405	0.467949	0.222402	0.26483	0.122987
Model 3	Arms fat	0.544081	0.439708	0.38584	0.393826	0.163326
	Legs fat	0.554125	0.351949	0.268305	0.288318	0.014756
	Head fat	0.726267	0.323147	0.382425	0.375402	0.079969
	Trunk fat	0.473539	0.211743	0.336407	0.297309	0.137372
Model 4	Arms fat	0.680244	0.726475	0.388133	0.510217	0.219764
	Legs fat	0.65909	0.580596	0.282283	0.370885	0.014371
	Head fat	0.717523	0.279476	0.351596	0.352545	0.10007
	Trunk fat	0.774093	0.859694	0.314675	0.566029	0.126853

Model1: age,sex adjusted

Model2: age, sex, smoking, alcohol drinking habit, physical activity, income and education adjusted

Model3: age, sex and total fat djusted

Model4: age, sex, smoking, alcohol drinking habit, total calorie intake, physical activity, income, education and total fat adjusted

5. Heritability showing genetic influence.

Table 5 and 6 display the heritability of fat obtained by using various component model. Table 5 shows the heritability of 4 regional fat distribution after adjusting age and sex and table 6 shows the heritability adjusted by age, sex and total fat (kg).

In the table 5, the best fitting models of regional fat were AE model except head fat; the best fitting model of head fat was ACE model. The result shows that the values of additive effect genetic effects were high from 0.64 to 0.62.

Although results of table 6 were lower than those of table 5, the values were still quite high (0.41-0.68). The best fitting models of 3 regional fat, arms, head and trunk, were ACE model, while the best fitting model was AE model on leg fat. In this table, because total fat explained many proportions of regional fat, variance by covariate was high; the range of the values was from 0.94 to 0.63. However, additive genetic effects were still high and common shared environmental effects (C) were less than additive genetic effect (A) in ACE model among the rest of variance excluding variance explained by covariate.

Among 4 regional fat, the heritability of legs fat was higher than other fat after adjusting age, sex and total fat mass (kg).

Table 5 Heritability of 4 regional fat adjusted by age and sex

Trait	Best fitting model	A (S.E.)	C (S.E.)	E	Variance by covariate
Arms fat	AE	0.62** (0.03)		0.38	0.20
Legs fat	AE	0.64** (0.03)		0.37	0.33
Head fat	ACE	0.62** (0.05)	0.10* (0.04)	0.28	0.46
Trunk fat	AE	0.64** (0.03)		0.36	0.06

Adjusted by age and sex

A : additive genetic effects, C: shared environment effects within family E: Unique environmental effects

**p value <0.01 *p value <0.05

Table 6 Heritability of regional fat adjusted by age sex and total.

Trait	Best fitting model	A (S.E.)	C (S.E.)	E	Variance by covariate
Arms fat	ACE	0.41** (0.05)	0.28** (0.04)	0.31	0.82
Legs fat	AE	0.68** (0.03)		0.32	0.86
Head fat	ACE	0.54** (0.05)	0.17** (0.04)	0.29	0.63
Trunk fat	ACE	0.64** (0.05)	0.10* (0.04)	0.26	0.94

Adjusted by age, sex, and total fat mass (kg)

A : additive genetic effects, C: shared environment effects within family E: Unique environmental effects

**p value <0.001 *p value <0.01

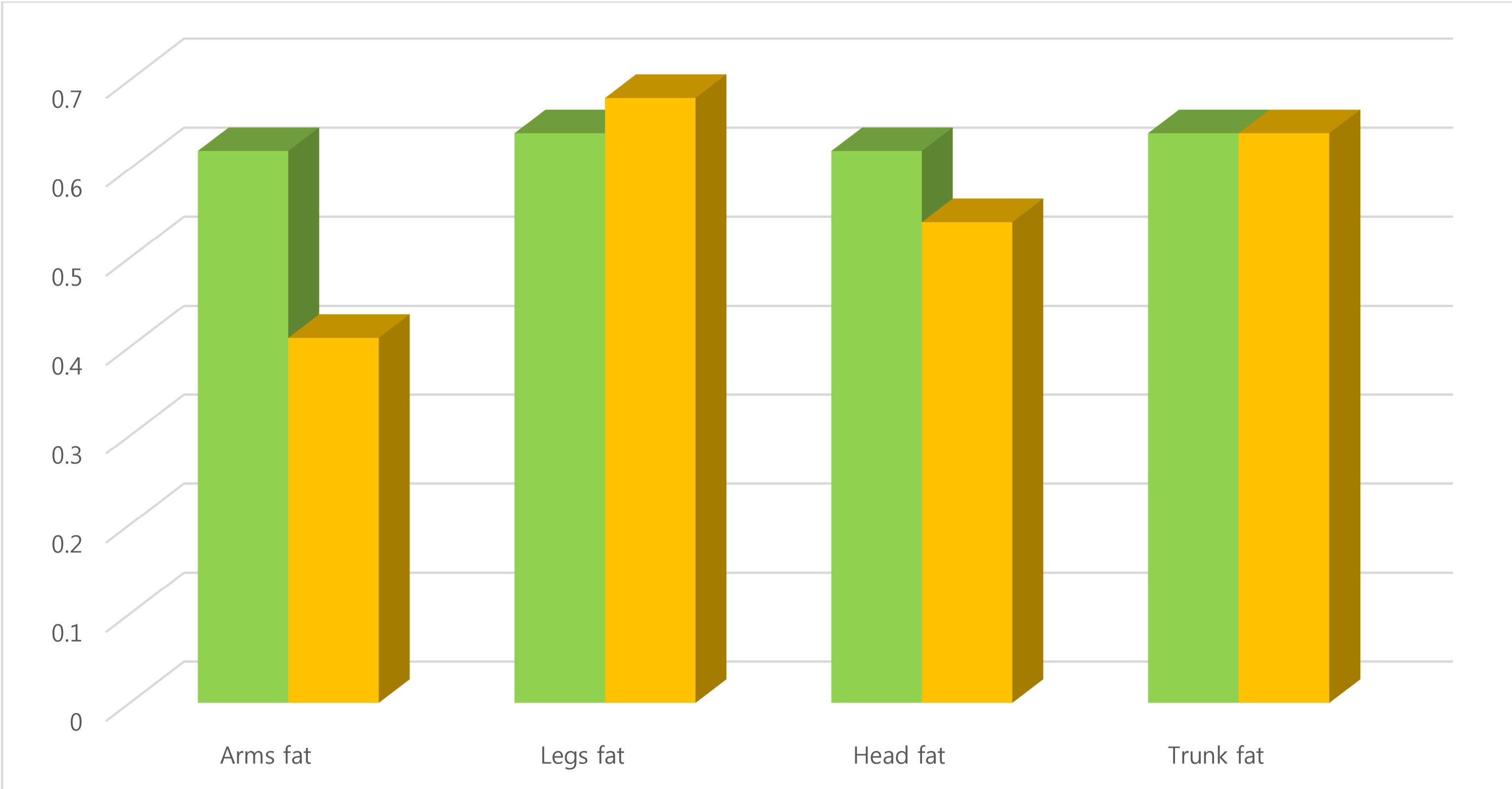


Figure 2. Comparing Heritability adjusted age and sex with Heritability adjusted age, sex, and total fat Green (left): after age and sex, yellow (right): after age, sex, and total fat. Although variance explained by covariate was high after adjusting total fat, the heritability was similar with the results with adjusting only age and sex.

Discussion

Until now, this study investigates environmental factor and genetic factor that have effects on regional fat distribution. Our study suggests that regional fat is mainly influenced by genetic factor more than environmental factor.

Regional fat mass was clearly different between male and female. There is interesting fact that female group has more arms, legs and trunk fat than male group. But, in head fat, male group has more fat than female group. This could be because male and female group have different body frame or because male- specific hormones play an important role.

Among several environmental factors, education is clearer than other variables. Especially, men who have the lower the education level have the more fat, whereas women have more fat in high education group. However, this study shows that environmental factors associated with 4 regional fat definitely were not found. In this respect, this result has something in common with another study using BMI and WC. They produce evidence on strong genetic influence in spite of obesogenic environment in children of their study(29).

Also, our study represent that genetic factor was associated with regional fat distribution. Results on the intraclass correlation coefficient (ICC) support that there is strong association between regional fat distribution and genetic factor. Because ICC infers the degree of resemblance within groups, people having high value of ICC resemble more each other. According to ICC results, monozygotic twin group has higher ICC value than dizygotic twin group. Because the difference between monozygotic twin and dizygotic twin is regarded as difference of genetic factor; decreasing values from MZ to DZ and sibling group in our study represents that resemblance of genetic factor is associated with 4 regional fat distribution.

The heritability analysis also provides evidence that genetic factors influence regional fat. In the table 6, although variance by covariate was very high; 0.63-0.94, the values of heritability (additive genetic effects) were also very high; 0.41-0.68 after adjusting age, sex, and total fat (kg). This means that genetic factor still affects regional fat excluding effects of total fat.

In addition to these results, common shared environmental effects in ACE model were about 0.1-0.2 and unique environmental effects were about 0.2-0.3. This suggests environmental effects on regional fat distribution might be weak and supports results of multiple regression (Table 3).

However, this study has limitation that the number of dizygotic twins is fewer than monozygotic twin. In regards to ICC analysis, the value could be underestimated. Also, environmental effects were few in this study. This is because environmental factors could be not actually associated with regional fat distribution or because the number of samples by category was not balanced. Therefore, more sophisticated study was needed to decrease probable errors.

Among the studies of fat distribution, there was genome-wide association study of body fat distribution. The samples consist of African ancestry and European ancestry in that study. The study identified some SNPs associated with fat distribution (21). However, we have not known SNPs associated with regional fat distribution because this study used WHR as fat distribution concept.

Our study suggests possibility of genome-wide association study and this further study could disclose what genetic factor is associated with regional fat distribution and what process regulates regional fat distribution.

Meanwhile, M. Cnop et al reported relationship between insulin sensitivity and fat distribution. The study suggests intra-abdominal fat used as research subject of fat distribution could be linked with insulin resistance and an atherogenic lipoprotein profile (30). Bernard et al reported that fat distribution has small independent effect on cardiovascular risk factor (8, 9, 14)and Elizabeth et al also used body fat distribution concept to investigate risk factors of breast cancer(9). In 1997, Vincent et al researched relatioship between WHR and non-insulin dependent diabetes (31). However, we should research again these topics with fat distribution by body composition because almost studies dealt with abdominal fat as fat distribution. Though overall fat distribution by body composition has not studied well, there are some studies dealing with body composition fat; Marieke et al studied that trunk fat and leg fat have relationship with fasting glucose level(32) and Teixeira et al researched limbs fat mass was not superior in predicting metabolic disturbances compared with BMI or central fat(33). Therefore, it’s necessary to study similar topics in terms of regional fat by composition for understanding overall fat distribution on our body.

Conclusion

Regional fat distribution by body composition has been curious phenotype with obesity. Many people think regional fat distribution would be inherited. In other words, genetic factors could regulate regional fat distribution. This study used arms, legs, head, and trunk fat as phenotypes. Notable environmental effects on fat distribution by body composition were not found. Meanwhile, the results of ICC and heritability analysis support that genetic components have effects on fat distribution. This means the popular belief that regional fat pattern would be inherited was found to be true. Therefore, this result makes us understand overall fat distribution and identify reasons that regional fat distribution is different between each person Furthermore, this could provide directions in managing regional fat among people and evidence for investigating what genetic factor influence on fat distribution. And, performing genome-wide association analysis would be needed as a follow-up study.

Reference

1. Alaitz Poveda MEIne, and Esther Rebato. Heritability and genetic correlations of obesity-related phenotypes among Roma people. Annals of Human Biology. 2012;39(3):183-9.

2. Marjaana Lahti-Koski PP, Markku Heliövaara, and Erkki Vartiainen. Associations of body mass index and obesity with physical activity, food choices, alcohol intake, and smoking in the 1982–1997 FINRISK Studies. Am J Clin Nutr. 2002;vol. 75(No. 5): 809-17.

3. Jane Wardle JW, and Martin J. Jarvis. Sex Differences in the Association of Socioeconomic Status With Obesity. American Journal of Public Health 2002;Vol 92(No. 8):1299-304.

4. Karoline Schousboe GW, Kirsten O. Kyvik, Jakob Mortensen, Dorret I. Boomsma. Sex Differences in Heritability of BMI: A Comparative Study of Results from Twin Studies in Eight Countries. Twin Research. 2003;6(5).

5. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007 May 11;316(5826):889-94. PubMed PMID: 17434869. Pubmed Central PMCID: 2646098.

6. Gerken T, Girard CA, Tung YC, et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science. 2007 Nov 30;318(5855):1469-72. PubMed PMID: 17991826. Pubmed Central PMCID: 2668859.

7. Martha L Slattery AM, Diane E Bud, Bette J Caan, Joan E Hilner, David R Jacobs Jr, and Kiang Liu. Associations of body fat and its distribution with dietary intake, physical activity, alcohol, and smoking in blacks and whites. Am J Clin Nutr. 1992;55:943-9.

8. Bernard Marti JT, Veikko Salomaa, Leena Kartovaara, Heikki J Korhonen,, Pietinen P. Body fat distribution in the Finnish population: environmental determinants and predictive power for cardiovascular risk factor levels. J Epidemiol Community Health. 1991;45: 131-7.

9. Elizabeth Sonnenschein PT, Mary Beth Terry, Peter F Bruning, Ikuko Kato, Karen L Koeing and Roy E Shore. Body fat distribution and obesity in pre- and postmenopausal breast cancer. Int J Epidemiol. 1991;28:1026-31.

10. Kang SM, Yoon JW, Ahn HY, et al. Android fat depot is more closely associated with metabolic syndrome than abdominal visceral fat in elderly people. PloS one. 2011;6(11):e27694. PubMed PMID: 22096613. Pubmed Central PMCID: 3214067.

11. Elissa S. Epel BM, Teresa Seeman, and Jeannette R. Ickovics. Stress and Body Shape: Stress-Induced Cortisol Secretion Is Consistently Greater Among Women With Central Fat. Psychosomatic Medicine. 2000;62:623-32.

12. Dexter Canoy NW, † Robert Luben,* Ailsa Welch,* Sheila Bingham,‡ Nicholas Day,* and, Khaw* K-T. Cigarette Smoking and Fat Distribution in 21,828 British Men and Women: A Populationbased Study. OBESITY RESEARCH. 2005;Vol. 13(No. 8):1466-75.

13. Rebecca J Troisi JWH, Pantel S Vokonas, and Scott T Weiss. Cigarette smoking, dietary intake, and physical activity: effects on body fat distribution-the Normative Aging Study. Am J Clin Nutr. 1991;53:1104-11.

14. Tracy L Nelson, Geor ge P Vogl er, Nancy L Peder sen, et al. Genetic and environmental influences on body fat distribution, fasting insulin levels and CVD: are the influences shared? Twin Research. 2000;3:43-50.

15. Bamia C, Trichopoulou A, Lenas D, et al. Tobacco smoking in relation to body fat mass and distribution in a general population sample. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2004 Aug;28(8):1091-6. PubMed PMID: 15197410.

16. Guagnano MT PV, Murri R, Marchione L, Merlitti D, Sensi S. Many factors can affect the prevalence of hypertension in obese patients: role of cuff size and type of obesity. Panminerva Medica 1998;40(1):22-7.

17. Arnaud Chiolero DF, Fred Paccaud, and Jacques Cornuz. Consequences of smoking for body weight, body fat distribution, and insulin resistance. Am J Clin Nutr. 2008;87:801-9.

18. Dirk L. Christensen JE, Andreas W. Hansen, Melanie W. Larsson, and Henrik Friis. Obesity and regional fat distribution in Kenyan populations: Impact of ethnicity and urbanization. Annals of Human Biology. 2008;35(2):232-49.

19. Ole Lander Svendsen CH, and Claus Christiansen Age- and Menopause-Associated Variations in Body Composition and Fat Distribution in Healthy Women as Measured by Dual-Energy X-Ray Absorptiometry Metabolism. 1995;Vol 44(No. 3):369-73.

20. Charlotte Malis ELR, Pernille Poulsen, Inge Petersen, Kaare Christensen,Henning Beck-Nielsen,‡ Arne Astrup, and Allan A. Vaag. Total and Regional Fat Distribution is Strongly Influenced by Genetic Factors in Young and Elderly Twins. OBESITY RESEARCH. 2005;Vol. 13(No. 12):2139-45.

21. Ching-Ti Liu LM, Caroline S. Fox. Genome-Wide Association of Body Fat Distribution in African Ancestry Populations Suggests New Loci. PLOS Genetics. 2013;9(8).

22. K. SAMARAS TDS, T. V. NGUYEN, K. BAAN, L. V. CAMPBELL, AND P. J. KELLY. Independent Genetic Factors Determine the Amount and Distribution of Fat in Women after the Menopause. JCE&M. 1997;82(3):781-5.

23. Ge´ orgia G. Pena MıSD, Andrea Gazzinelli, Rodrigo Corrˆ ea-Oliveira and Gustavo Velasquez-Melendez. Heritability of Phenotypes Associated with Glucose Homeostasis and Adiposity in a Rural Area of Brazil. Annals of Human Genetics. 2014;78:40-9.

24. Bogaert V, Taes Y, Konings P, et al. Heritability of blood concentrations of sex-steroids in relation to body composition in young adult male siblings. Clinical endocrinology. 2008 Jul;69(1):129-35. PubMed PMID: 18598274.

25. I. GUERRINI CG, and M. GUAZZELLI. ALCOHOL CONSUMPTION AND HEAVY DRINKING: A SURVEY IN THREE ITALIAN VILLAGES. Alcohol & Alcoholism. 2006;41(3):336-40.

26. WHO. International Guide for monitoring alcohol consumption and related harm . 2000.

27. Ainsworth BEH, William L. Herrmann, Stephen D. Meckes, Nathanael Bassett, David R. Tudor-Locke, Catrine Greer, Jennifer L. Vezina, Jesse; Whitt-Glover, Melicia C. Leon, Arthur S. . "2011 Compendium of Physical Activities". Medicine & Science in Sports & Exercise. 2011;43(8):1575-81.

28. Adrian Bauman FB, Tien Chey, Cora L Craig, Barbara E Ainsworth, James F Sallis, Heather R Bowles, Maria Hagstromer, Michael Sjostrom, Michael Pratt and The IPS Group. The International Prevalence Study on Physical Activity: results from 20 countries. International Journal of Behavioral Nutrition and Physical Activity. 2009:6-21.

29. Jane Wardle SC, Claire MA Haworth, and Robert Plomin. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. Am J Clin Nutr. 2008;87:398-404.

30. Cnop M, Havel PJ, Utzschneider KM, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia. 2003 Apr;46(4):459-69. PubMed PMID: 12687327.

31. VincentJ .Carey, EllenE.Walters, GrahamA.Colditz, et al. Body Fat Distribution and Risk of Non-lnsulin-dependent DiabetesMellitus in Women. Am J Epidemiol. 1997;Vol145(No.7):614-9.

32. Marieke B. Snijder JMD, Marjolein Visser,Lex M. Bouter, Coen D.A. Stehouwer. Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels DIABETES CARE. 2004;27(2).

33. Pedro J. Teixeira LBS, Scott B. Going, and Timothy G. Lohman. Total and Regional Fat and Serum Cardiovascular Disease Risk Factors in Lean and Obese Children and Adolescents. OBESITY RESEARCH. 2001;9(8):432-42.

Table S 1. Correlation between legs fat and sitting time

	Leg fat					
	Total	Pvalue	Male	Pvalue	Female	Pvalue
Sitting time (hour)	0.03654	0.0322	0.0885	0.0009	0.04873	0.028
Education group	0.07096	<.0001	0.16953	<.0001	0.08842	<.0001

Sitting time (hour) ; sitting time for week days (hour/a week)
Education group divided by high school graduation

Abstract in Korean (국문초록)

지방 분포와 관련된 유전 및 환경적 요인 분석

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사람들은 흔히 자신들은 부위마다 지방의 분포가 다르고 이것은 특히나 유전적일 것이다라는 생각을 가지고 있다. 또한 이러한 부위마다 다른 지방 관리의 방법들도 다양하게 존재하고 있다. 하지만 정작 부위별 지방분포에 대한 논문들을 찾게 되면 복부비만과 관련한 논문들이 주요하다. 복부비만의 경우, 비만과 관련된 질병들의 주요 원인이다. 이에 따라 복부비만의 연구들이 주요하게 이루어져 왔고, 실제적으로 다른 부위별 지방 분포와 관련한 연구는 매우 부족한 상황이다.

본 연구는 한국 가족 쌍둥이 코호트에 참여하고 있는 3461 명들 중 Dual-energy X-ray absorptiometry (DXA) 계측이 되어 있는 3435명을 이 연구에 포함 시켰다. 이들 중 가족은 689 가족, 일란성 쌍둥이는 550 쌍, 이란성 쌍둥이는 124 쌍이 포함되었다. 그리고 DXA 계측이 되어 있는 부위는 양쪽 팔, 양쪽 다리, 머리, 몸통으로 이들 부위의 자료들

을 가지고 연구를 진행하였다. 여러 부위의 fat mass와 비만 지수들간의 연관성은 spearman correlation 분석방법을 사용하였다. 부위별 지방 분포와 여러 환경적인 요인들의 분석은 mixed model 을 이용한 multiple regression 방법을 사용하여 분석하였다. 부위별 지방분포의 유전적인 요인은 intraclass correlation coefficients (ICC) 와 variance component model을 이용한 유전율 분석을 가지고 분석하였다.

연구결과 부위별 지방분포와 복부비만의 중요한 지표인 waist hip ratio 의 값은 관련성이 적다는 것과 부위별 지방 분포가 환경적인 요인과는 관련성이 적다는 것을 알 수 있었다. 하지만 부위별 지방의 환경적인 관련성은 낮지만 유전적인 요인들과의 관련성을 분석한 결과, 상당한 관련성이 있음을 알 수 있었다. 이것은 ICC 분석과 유전율 분석 모두에서 확인해 볼 수 있어 특히 유전율 분석에서 전체 지방은 여전히 부위별 지방 분포에 관해 많은 부분을 설명하고 있지만 이러한 효과를 제외하고 나머지 효과에 대한 유전적인 영향은 여전히 매우 높았다. 이것을 통해 부위별 지방에 영향을 미칠 수 있는 여러 요인들 중 유전적 요인이 지방 분포에 대한 유의미한 영향을 미치고 있다고 보여지고 부위별 살찌는 체질이 유전적으로 내려온다는 통념을 어느 정도 설명해준다.

이러한 본 연구 결과는 복부비만이 주가 되었던 지방분포 연구에서 부위별 지방 분포에 대한 연구를 통해 한국인의 전체적인 지방분포에 대한 이해도를 높일 수 있을 것이다. 또한 이 연구결과 유전적인 영향 큰 것으로 보이는데 이에 대해 지방분포와 호르몬의 관계성 또는 지방 분포에 대한 genome-wide association study 등 이 연구뿐 아니라 이와 관련한 후속 연구들을 통해 부위별 지방의 관리에 대한 방향성을 제시할 수 있을 것이다.

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주요어 : 부위별 지방, DXA, 환경적 요인, 유전율, 가족 쌍둥이 분석

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